

REMARKS

The Final Office Action of September 29, 2003, has been received and reviewed. Claims 1-11, 14-16, 18, and 21-25 are pending in the application and all claims stand rejected. Claims 1, 3-11, 14-16, 18, and 21-25 have been amended and claim 2 has been canceled as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11, 15-18, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Applicants respectfully traverse the rejections as set forth herein.

Applicants note that the Advisory Action of February 13, 2004 indicated that “if the amendment were entered, the rejection of claim 11 under 35 U.S.C. § 112, 2nd paragraph would be overcome.” (Advisory Action of February 13, 2004, page 2). Support for the amendment is found, *inter alia*, at paragraph [0019] of the as-filed specification.

With regard to claim 15, although applicants do not agree that claim 15 is indefinite, claim 15 is amended to be directed towards a method of screening for agonists of a chimeric receptor wherein the method includes identifying the at least one compound that binds to said chimeric receptor and activated said autocrine loop, thereby identifying the antagonist of the chimeric receptor as discussed with the Examiner in a telephone conference on March 9, 2004. Support for the amendment to claim 15 is found, *inter alia*, at paragraphs [0013], [0015] and [0016] of the as-filed specification. Thus, claim 15 should be definite.

With regard to claims 24 and 25, indefinite rejections of record were maintained since it was thought “the claims are indefinite because the steps recited by the methods do not necessarily achieve the goal set forth in the preamble.” (Final Office Action at page 2). The Final Office Action stated “the method steps never require measuring and/or comparing the binding of a ligand to a chimeric receptor in the presence or absence of a test compound” (*Id.* at page 3) and the Advisory Action of February 13, 2004 indicated that “activation or deactivation of the reporter system is not an indicator of whether a compound (an antagonist) binds to a

chimeric receptor.” (Advisory Action at page 2). Although applicants do not agree with the rejections, to expedite prosecution, claims 24 and 25 have been amended as set forth herein.

Amended claim 24 recites in part determining the ability of the compound to activate the reporter system, comparing the ability of the compound to activate the reporter system to a positive or a negative control, thereby identifying the antagonist of the chimeric receptor in accordance with the comments from the Examiner during the telephone conference of March 9, 2004. Support for the amendments is found, *inter alia*, at paragraphs [0019], [0058], [00105] and [00112] of the as-filed specification.

With regard to claim 25, it has been amended to recite in part contacting the compound with said chimeric receptor in the presence of a ligand of the chimeric receptor, assaying the inhibiting activity of the ligand-receptor binding by assaying the activation of the reporter system, comparing the inhibiting activity of said series of compounds to a positive or a negative control, and determining the presence of an antagonist that creates said anti-autocrine loop by scoring the deactivation of the reporter in accordance with the comments from the Examiner during the telephone conference of March 9, 2004. Support for the amendments is found, *inter alia*, at paragraphs [0019], [0058], [00105] and [00112] of the as-filed specification. Thus, as amended, claim 25 should be definite.

Reconsideration and withdrawal of the indefiniteness rejections of claims 11, 15-18, 24 and 25 are requested.

Rejections under 35 U.S.C. § 103

Claims 1-6, 10, 11, 14-16, 18 and 21-25 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Pestka *et al.* in view of Trueheart *et al.* Applicants respectfully traverse the rejections as set forth herein.

A *prima facie* case of obviousness cannot be established with regard to any of independent claims 1, 15, 24 or 25 as amended, since the cited references do not, alone or in combination, teach or suggest each and every element of any of the independent claims or any of the claims depending therefrom. For instance, the asserted combination of the chimeric receptor

of Pestka *et al.* with the yeast cells of Trueheart *et al.* does not result in the cells recited in any of independent claims 1, 15, 25 or 25.

Further, no suggestion or motivation exists to combine the cited references since one of ordinary skill in the art would not be motivated to combine the chimeric receptor of Pestka *et al.* with the yeast cells of Trueheart *et al.* However, in order to expedite prosecution, applicants each of independent claims 1, 15, 24 and 25 has been amended as set forth herein.

As amended, each of independent claims 1, 15, 24 and 25 includes an element directed to a **mammalian** cell, and not to **any eukaryotic** cell. Support for the amendments is found, *inter alia*, at paragraph [0013] of the as-filed specification.

Since each of the working examples of Trueheart *et al.* is limited to the use of yeast cells, one skilled in the art would not reasonably expect the chimeric receptor of Pestka *et al.* to function in the yeast cells of Trueheart *et al.* For instance, one skilled in the art would not expect the autocrine loops including the G-protein coupled receptors (GPCRs) of the yeast cells Trueheart *et al.* to function in the cells of Pestka *et al.* in the same manner as a test compound exogenously added to a cell since the cells of Pestka *et al.* include several hundreds of GPCRs. “One factor which can complicate the use of heterologous expression systems for ligand fishing involves the presence of endogenous receptors in **mammalian cell lines** and in particular, clonal variation in the pattern of endogenous receptor expression in cells derived from the same parental cell line.” (Wilson et al., *Orphan G-protein-coupled receptors: the next generation of drug targets?*, *British Journal of Pharmacology*, vol. 125, 1387-1392, at p. 1389 (1998) (previously submitted) (emphasis added)). Further, “the ability to genetically delete endogenous GPCRs from **yeast** to generate a ‘null’ background is one of the major advantages in using yeast model systems for orphan receptor screening.” (*Id.* at 1390) (emphasis added). Thus, the background expected from the presence of a gene encoding a test compound in the mammalian cells of Pestka *et al.* would frustrate selection.

Trueheart *et al.* recognized this problem by reciting “it will be understood to achieve selection or screening, the host cell must have an appropriate phenotype. For example, generating a pheromone-responsive chimeric HIS3 gene in a yeast that has a wild-type HIS3 gene would frustrate genetic selection.” (Trueheart et al., page 20). Thus, Trueheart *et al.*

recognized that the wild-type gene would frustrate genetic selection because of the background produced by the wild-type gene and, thus, teaches away from combining the teachings of Trueheart *et al.* with Pestka *et al.*.

Additionally, since the receptors of Trueheart *et al.* are functionally integrated in the signaling pathway, *e.g.*, the endogenous signaling pathway (*See, Trueheart et al.*, page 16, line 26 through page 17, line 1), the chimeric receptor of Pestka *et al.* would not be expected to work in the yeast cells of Trueheart *et al.* without undue experimentation or testing. Further, the article submitted herewith provides additional evidence that the autocrine loop of Trueheart *et al.* would not be expected to work with the mammalian cells of Pestka *et al.* The article indicates that even when IL3 (the ligand) is internally produced in the cell, the autocrine loop is not stimulated. The cells are dependent on the exogenous addition of IL3 suggesting that the interaction of a ligand and a receptor in the cell are required instead of the mere presence of the ligand in the cell. (*See, Mechanism of Autocrine Stimulation in Hematopoietic Cells Producing Interleukin-3 after Retrovirus-Mediated Gene Transfer*, Browder *et al.*, Mol Cell Biol. 1989 Jan; 9(1): 204-13) (attached hereto)). The applicant may “cite references to show what one skilled in the art knew at the time of filing the application.” (M.P.E.P. § 2164.05)

Accordingly, reconsideration and withdrawal of the obviousness rejections of claims 1-6, 10, 14-16, 18 and 21-25 are requested.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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